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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,592	07/13/2001	Keiya Ozawa	50026/012003	6387

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	09/905,592	OZAWA ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 5,6,8-15 and 17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 5,6,8-15 and 17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant has elected Group I in response to a restriction requirement. It is acknowledged that applicant has submitted an amendment to claim 5. Upon reconsideration and given applicant's argument filed 07/28/03 the restriction is withdrawn. The claims examined in this action are claims 5, 6, 8-15 and 17.

Drawings

New corrected drawings are required in this application because the *lines* in Fig(s) 1, and 4-9 are poor in quality (see attached Form 948). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. **The claimed invention is directed to non-statutory subject matter, in claims 6 and 15.**

Claims 6 and 15 recite a "cell" containing nucleic acid vectors. However, the recited cells containing the claimed nucleic acid vectors can be in a human since the specification contemplates use of the invention to treat disorders in humans, hence the claims read on a part of

a human (or the whole person) having the cell within his/her body. Claims reading on humans are non-statutory. It would be remedial to include "isolated" before cell to obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. **Claims 6, 9-12 and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention.**

Claims 9-12, respectively referring to proliferation domain and ligand-binding domain, indicate that each domain is derived from a cytokine or hormone receptor. It is not clear what the phrase "derived from" means, because the relationship between the starting material (ctyokine receptor) and the recited domain is unclear. How closely related to the starting material does the domain need to be in order to be "derived from" said material. The metes and bounds of the claimed subject matter are unclear.

Claims 14 are indefinite and unclear because the claim language indicates that the gene encoding a fusion protein and an exogenous gene are either on the same or separate molecules respectively. There is added confusion because the independent claim indicates a single vector while dependent claim 14 alludes to two vectors (as such claim 14 is not further limiting the base claim). For the purposes of examination the dependent claim 14, will be interpreted to mean two separate vectors, comprising two separate genes (i.e. exogenous and fusion gene).

Both claims 6 and 15 recite a cell. The recited "cell" can be in an in vitro environment. If it is in an in vivo environment, it is unclear what applicants are claiming because the cell

would be a part of the animal or human, i.e. are applicants claiming the cell within an animal or human or the entire animal or human containing the cell because the cell is part of the host organism. It would be remedial to include "isolated" before cell to clarify the metes and bounds of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claim 5-6, 8-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

The independent claims are drawn to a limitless number of fusion constructs comprising the vector composition being claimed. In addition claim 17 is drawn to a limitless number of ligands. The various constructs can comprise wild type as well as mutated versions for each of the three domains claimed (i.e. ligand-binding, associating and proliferation domains). The amino acid composition from one fusion construct to another can vary widely, as can the structure and composition of cognate ligands. The specification does not provide an adequate disclosure of species that fall within the claimed genera of domains or ligands, such that a skilled artisan would be able to distinguish amongst those that fall within the claims from those that fall without.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

Applicant's specification provides a single example of Ba/F3 cells transformed with fusion constructs contained on a transforming vector, where one type of proliferation domain (i.e. G-CSF receptor) and one type of ligand-binding domain (i.e. estrogen receptor domain). There is no other disclosure as to the genera of domains claimed; for these additional species within the separate genera, applicant only recites the claimed domains by functional means without any disclosure as between the limitless number of structures and the correlative function. For example a single amino acid mutation may confer specificity for an altogether different ligand (i.e. for the ligand-binding domain). Moreover, ligand-binding domains are not amenable to mutational analysis due to the complexity of tertiary folding (*see*, O'Malley et al. US 6,416,998, col. 3, ll. 54-64; hereinafter, '998 or '998 patent). Similarly, the associating domains (e.g. DNA binding domains) are susceptible to specific structural modification resulting in a materially different result functionally. It must therefore be considered that the single disclosed species is not a representative number of species sufficient to convince the skilled artisan that applicant is in possession of the claimed genus.

Furthermore, considering the scope of the claims, having a handful of examples would not be sufficient to support the contention that applicant is in possession of the various genera being claimed.

4. **Claims 5-6, 8-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

While the claims are drawn to a composition there remains a requirement that the specification must teach the skilled artisan how to use the claimed composition. The specification discloses that the only contemplated use of the claimed vector (and cells) is in gene therapy, thus the claims read on gene therapy vectors.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims: The claims' scope is wide and deep. The invention is drawn to three separate domains each with particular function.

Within each domain there is a virtually limitless number of possible constructs. In addition the invention is drawn to gene therapy, which can involve complex multi-factorial pathways in the body.

Nature of the invention: The invention is drawn to vector constructs comprising three separate functional domains (i.e. ligand-binding, associative and proliferation). Each domain has a particular function, which may be repressed or enhanced by various factors in the cell. Regulation of cell activities, that could for example lead to cell proliferation, is often coupled to secondary messengers or cofactors (e.g., ligand-induced tyrosine kinase activity).

In addition the claims directly implicate gene therapy since independent base claims recite, "impart[ing] proliferation activity" to the affected cells, and is further evidenced by applicant's full disclosure that the vectors' contemplated use is in gene therapy.

Unpredictability of the art: The invention inheres a great deal of unpredictability on two different levels. First, there is unpredictability in that the fusion proteins encoded on the vector constructs, when expressed in the cell or in the body may be toxic to the cell or host. In addition the various domains may not fold properly in the cell, due to particular structural differences (e.g., a single amino acid variation could cause a different tertiary conformation altogether). Furthermore, one or more of the domains encoded on the vector construct may function inadequately or not at all.

On a second level, gene therapy is still a highly unpredictable art within biology and medicine. For example, vectors used to deliver constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Feb. 13, 2003, Nature, 421: 678) (citing occurrence of leukemia due to insertion

of retroviral vectors used in gene therapy into a particular stretch of DNA); (*see also*, Juengst, ET. June 2003, BMJ, 326:1410-11) (indicating that gene transfer often has multiple and unpredictable effects on cells). Furthermore gene therapy is a highly unpredictable art with poor efficiency of delivery of the transgene to the target cells, poor transformation efficiency of target cells, unpredictable and transient expression of the transgene in target cells, etc. *See*, Kmiec, American Scientist, 1999, Vol. 87: 240-147; Anderson, Nature, 1998, Vol. 392: 25-30; Verma et al., Nature, 1997, Vol. 389: 239-242 (reviewing the multitude of difficulties and lack of success in gene therapy methods).

Applicant contemplates using vectors to transfect cells either *in vivo* or *ex vivo* (i.e., to cause cell proliferation, claims 5 and 8). Regardless, if cells are transfected in the body or transfected cells are then transplanted in the body, there is high degree of unpredictability as to what effects are imparted directly, via the vectors or the proteins they encode.

State of the art: The state of art is poorly developed. Although some factors have been characterized that impart cell-selective proliferation activity, it is an entirely different proposition to use vector constructs encoding such factors in gene therapy.

Amount of guidance provided: Applicant provides some generic guidance as to sources of ligand-binding, associative and proliferation domains. There is no guidance as to obstacles that would be faced in conducting gene therapy using the invention.

Number of working examples: There is a single example of a construct encoding the multi-domain fusion protein. There are no examples of using said construct *in vivo*.

Level of Skill in the art: The level of skill in the art is high. However, there are unsolved hurdles to successfully practicing gene therapy, as well as unpredictability in the art,

little guidance and a single working example, therefore it must be considered that the skilled artisan would have to conduct trial and error experimentation in order to attempt to practice the claimed invention.

Given the above analysis of the factors that the courts have determined are critical in ascertaining whether the claimed invention is enabled, it is considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

Generally where a claim is rejected for lack of enablement, it might seem inconsistent to apply an art rejection. However, such is not the case where the enablement rejection is based on the instantly disclosed use for a composition and the prior art is applied to the composition itself. The analysis is wholly separate, thus it is appropriate to apply both an art and an enablement rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. **Claims 5-6, 8, 11-13 and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Littlewood et al. (Nuc. Acids Res. June 1995, 23(10): 1686-90 (see whole document) [hereinafter Littlewood].**

The claims are drawn to a fusion construct and cells containing the same, where the fusion construct encodes a fusion protein having three domains (i.e. ligand-binding, associative and proliferation). Furthermore the ligand-binding domain is from a steroid hormone receptor, more specifically an estrogen receptor. In addition the invention is drawn to constructs where an exogenous gene is contained on the same vector as the fusion construct, where exogenous gene introduced into a cell is not particularly limited. (Spec. at 7, ¶ 2, last line).

Littlewood teaches a fusion construct encoding a fusion protein having a ligand-binding domain (i.e. estrogen receptor), an associative domain (i.e. helix-leucine-helix zipper) and a proliferation domain (i.e. c-Myc). (*See* p. 1687, Materials and Methods and Fig. 1). In addition the fusion construct is mobilized into a retroviral vector that contains exogenous genes. (*Id.* at 1687, ¶2, last sentence, reciting pBpuro vector as described in, Morgenstern and Land. 1990, Nucleic Acids Research, 18(12): 3587-96, at p. 3592, Fig. 5; showing the exogenous gene *puro*) (Note: this additional reference is only cited to show the intrinsic quality of the vector construct recited, *See* MPEP § 2131.01). In addition Littlewood teaches cells that are transfected with the fusion construct (i.e. fibroblasts). (p. 1687, col. 2, ¶ 1). Thus Littlewood anticipates claims 5-6, 8-13 and 15.

6. **Claims 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Roussel et al. (Proc. Natl. Acad. Sci. 1988, 85: 5903-7)(*see* whole document)[hereinafter Roussel]**

Roussel teaches a construct encoding a fusion protein that is expressed in mouse fibroblasts and induces cell proliferation. (*See* Abstract, p. 5904, Results ¶1 and p.5905 Fig. 1(i)-(l)). The construct has a ligand-binding domain (i.e. Colony Stimulating Factor – 1), an associative domain (i.e. v-fms kinase domain), which also induces cell proliferation. (*Id.*) Thus Roussel anticipates claims 5 and 6.

7. **Claims 5-6, 8-10, 13 and 15 are rejected under 35 U.S.C. 102(e) as being anticipatd by Greenberg et al. (US 5,747,292 with priority §371 date, May 31, 1994) (*see* whole document)[hereinafter '292 or '292 patent].**

The invention is drawn to tri-partite fusion construct as described above. In addition an exogenous gene can be on the same or separate vector molecule, which contains the fusion construct. Furthermore, the invention is drawn to the proliferative domain being a cytokine receptor. Claims are also drawn to cells containing the vector constructs.

The '292 patent teaches a DNA construct encoding chimeric receptors that enable activated lymphocytes to proliferate in response to a ligand bindind the cognate domain of the chimeric protein being expressed. (*See e.g.*, col. 4, ll. 13-18). Constructs expressed contain a cytoplasmic region from a cytokine receptor, e.g. GM-CSF (i.e. proliferative domain) joined via a transmembrane domain (i.e. associative domain), to an extracellular domain (i.e. ligand-binding domain). (col. 4, ll. 5-29). In addition '292 teaches that the fusion construct can be

mobilized into an expression vector containing an exogenous gene, e.g. *neo*, (col. 15, ll. 35-40) as well as cells containing said vector construct, e.g. T cells (col. 16, ll. 46-65). Therefore the claims cited above are anticipated.

8. **Claim 5-6, 8-10 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Roberts (US 5,686,281, continuation of US Application 383,749, filed Feb. 3, 1995) (*see* whole document)[hereinafter '281 or '281 patent].**

The invention is drawn to constructs and cells containing the same, where the constructs comprise three separate domains – ligand-bindg, associative and proliferative. Furthermore, the claims are drawn to the proliferation domain being derived from cytokine receptor, more specifically G-CSF. In addition the constructs can contain an exogenous gene on the same vector molecule.

The '281 patent teaches DNA constructs encoding chimeric (i.e. fusion) proteins comprising at least three domains in a single chain molecule: a ligand-binding domain, a transmemberane (i.e. associative) domain and a cytoplasmic co-stimulatory effector function-signaling domain (i.e. proliferation, col. 5, ll. 65-66). (*See* Abstract, Fig. 1, col. 3, ll. 13-15; col. 6, ll. 6-68). Furthermore '281 teaches that constructs can be transfected into cells (e.g. hematopoietic cells). (col. 15, ll. 64-67, bridging to col. 16, ll. 1-27). Furthermore the proliferative domain is a cytokine – CD28. (*See* col. 13, ll. 34-45 and Fig. 1A, 1B). '281 also teaches that chimeric receptors can include G-CSF. (*See e.g.*, col. 14, ll. 59-63).

In addition '281 teaches that the fusion constructs can be mobilized into retroviral vectors which would contain desired exogenous genes, such as selection markers. (*See e.g.*, col. 12, ll.

50-54; col. 15, ll. 6-11; col. 19, ll. 55-59). The '281 patent teaches mobilization of a fusion-construct into a retroviral vector – containing *gag*, *pol* and *env* genes (as described in, Finer et al. 1994, Blood, 83(1):43-50, at 44, Fig. 1; this reference is only being provided to show the intrinsic characteristic of the vector construct comprising an exogenous gene, *See* MPEP § 2131.01). Thus the '281 patent anticipates claims 5-6, 8-10 and 15.

9. **Claims 5-6, 8 and 11-15 are rejected under 35 U.S.C. 102(e) as being anticipated by O'Malley et al. (US 6,416,998, filed Jun. 7, 1995 as CIP of 07/939246 filed Sep. 2, 1992) (*see* whole document)[hereinafter '998 or '998 patent].**

The invention is drawn to constructs and cells containing the same, where the constructs comprise three separate domains – ligand-binding, associative and proliferative.

Furthermore, the claims are drawn to the ligand-binding domain being derived from a hormone receptor, more specifically estrogen receptor. In addition the constructs can contain an exogenous gene on the same or separate vector molecule. The invention is also drawn to a kit containing said vector constructs, as well as ligands.

'998 teaches chimeric constructs with a ligand-binding domain, associative domain (i.e. DNA binding domain) and a domain having transactivation or transrepressor activity, which can lead to cell proliferation. (*See e.g.*, col. 5, ll. 45-64; col. 7, ll. 51-65; col. 8, ll. 1-9; Figures 7-8 and 12; col. 36, ll. 1-9). Furthermore, the '998 patent teaches that the ligand-binding domain can be a steroid hormone receptor domain, more specifically an estrogen receptor. (*See e.g.*, col. 2, ll. 23-26; col. 8, ll. 64-67, bridging to col. 9, ll. 1-9).

Furthermore '998 teaches that cells can be transfected said constructs, thus carry the vectors (e.g. CV1 cells). (*See e.g.*, col. 28, ll. 14-41; col. 30, ll. 18-25). '998 also teaches that an exogenous gene can be contained on the same vector molecule, where constructs are mobilized into vector construct with an exogenous gene – chloramphicol acetyltransferase. (*See e.g.*, col. 22, ll. 60-65); or that multiple vector constructs containing the fusion construct and an exogenous gene can be co-transfected so that a target therapeutic gene, where separate vector molecule can contain a target sequence, i.e. desired exogenous gene (*See e.g.*, col. 38, ll. 59-62). In light of the foregoing teaching, '998 anticipates claims 5-6, 8 and 11-15.

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30.If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

DAVID GUZO
PRIMARY EXAMINER